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## EUROPEAN PATENT APPLICATION

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(10) Novel composition for skin penetration enhancement.

(11) A unique combination of Isopropyl and Isobutyl alcohols synergistically increases the permeability of the skin to steroid drugs.

## NOVEL COMPOSITION FOR SKIN PENETRATION ENHANCEMENT

This invention relates to the field of transdermal administration of drugs. More particularly, it relates to the enhancement of transdermal delivery of steroid drugs.

Transdermal administration of drugs offers several therapeutic and compliance advantages over the more traditional routes of administration. A major drawback of this therapy, however, is the limitation on the amount of drug that can be transported across the skin. This limitation is due to several factors. Since the skin is a protective barrier by nature, the rates of transport of most compounds through the skin are quite slow. Also, even though the skin is the largest single organ, there aren't many areas on the body where its surface is flat. Therefore, as a practical matter, transdermal drug delivery patches must have a relatively small surface area. It is generally accepted that a surface area of the patch beyond 30 to 50 cm<sup>2</sup> would result in difficulty of application due to the contours of the skin. Moreover, drug permeability varies greatly between skins of different individuals.

It is thus important to increase the rates of penetration of drugs across the skin so that a wider variety of drugs can be administered by transdermal therapy. While steroids are relatively poorly permeable to skin, it has become desirable to administer this class of drugs transdermally, and transdermal patches for delivery of steroids have become available.

Increasing the permeability of the skin to steroids would allow an increased degree of control in the system for drugs with moderate permeabilities.

Aliphatic alcohols are commonly used in topical-transdermal formulations as cosolvents. US Patent 4,480,372 makes use of ethanol as a permeation enhancer. UK Patent Application GB 2,158,355A discloses the use of a combination of propylene glycol and glycerine to enhance the transdermal penetration of therapeutic agents. US Patent 4,593,048 describes the use of a combination of a monohydric lower alcohol having 1 to 4 carbon atoms with at least one of (a) a saturated aliphatic hydrocarbon, (b) a carboxylic acid alcohol ester, and (c) an ether to improve skin permeation and percutaneous absorption of drugs.

The present invention makes use of a particular combination of isopropyl alcohol (IPA) and isobutyl alcohol (IBA) to enhance the transdermal penetration of steroids. More particularly, it has been found that, while use of either of these solvents alone does not enhance the penetration of estradiol through cadaver skin *in vitro*, when these solvents are used in combination in approximately equal amounts (w/w), the rate of penetration of estradiol is increased at least two-fold.

Thus, in one aspect, the present invention provides a topical composition for the transdermal delivery of a steroid drug which comprises a therapeutically effective amount of a steroid drug in a vehicle comprising a mixture of isopropyl alcohol and isobutyl alcohol, each of these alcohols being present in an amount of from 45% to 55% by weight based on the weight of said mixture.

In another embodiment, the invention provides a method for enhancing the rate of transdermal delivery of a steroid drug, this method comprising contacting the skin with a composition comprising said steroid and a vehicle which comprises a mixture of isopropyl alcohol and isobutyl alcohol, each of these alcohols being present in an amount of from 45% to 55% by weight based on the weight of said mixture.

In yet another embodiment, the invention comprises a device for transdermal delivery of a steroid drug, in which device the vehicle for the steroid drug comprises a mixture of IPA and IBA, each of these alcohols being present in an amount of from 45% to 55% by weight, based on the weight of said mixture.

A preferred steroid for use in the compositions and methods of the present invention is estradiol. For certain applications, it is desirable to use a combination of estradiol and a progestogen; such as progesterone or medroxyprogesterone.

The compositions of the present invention may also include, in the vehicle, in addition to the mixture of substantially equal amounts of IPA and IBA, other pharmaceutically acceptable carrier liquids compatible therewith and with the steroid or steroids employed. A particularly preferred additional carrier liquid is water, which is preferably present in an amount of up to 50% by weight, based on the total weight of the vehicle.

While the IPA and IBA may each be present in the mixture in an amount of from 45% to 55% by weight, based on the total weight of the mixture, it is preferred that the range be from 47% to 53%. More preferably, the range is from 49% to 51%.

It has been found that, when water is included in the vehicle, a gelling agent such as methocel (methyl cellulose) or PVP (polyvinylpyrrolidine) may also be included. Other commonly used adjuvants, such as antioxidants, surfactants and the like may also be incorporated in the vehicle.

Transdermal drug delivery devices in accordance with the present invention may comprise any conventional transdermal patch construction employing pharmaceutically acceptable materials that are compatible with the steroid drug and with the drug delivery vehicle comprising the IBA/IPA mixture of the

present invention (as described above). Typically, the device, or transdermal patch, will comprise an impervious backing layer, a drug containing layer comprising the steroid drug in admixture with a vehicle of the present invention, a spreading layer, an adhesive layer and a release lining. Selection of particular patch designs as well as of particular materials of construction will be routine matters to those skilled in the art.

5 The following examples are presented to illustrate the practice of the present invention.

Example I:

10 Table I shows the compositions of 5 test formulations. Each formulation contains a sufficient amount of estradiol to make a saturated solution of estradiol. Thus, the rates of penetration of estradiol through cadaver skin would be similar if the diffusivity of estradiol through the cadaver skin is the only controlling factor. However, Table II clearly shows that the rate of penetration of estradiol at least doubles when the solvent composition comprises a 50:50 w/w mixture of IP/IBA. The data shown in Table II were obtained  
15 by testing the formulations of Table I in accordance with the following procedure.

A piece of human cadaver skin was placed over the opening of a Franz extraction cell filled with saline solution, with the stratum corneum facing the donor compartment and the dermal side facing the receptor, and was set in place and stretched taut by inserting the glass ring (a glass cover with the center open to add sample) and clamping to hold in position. The skin was equilibrated to physiological saline overnight at  
20 37°C.

Samples of drug and skin penetration-enhancing agents having the compositions shown in Table I were prepared, and each formulation was tested by placing a 0.5 mL sample onto the skin through the opening in the ring that forms the top of the cell (after equilibration) sealing the cell with a screw cap, and allowing the extraction to continue for 7 days.

25 Periodically, the receiver solution in the cell was removed and replaced with fresh saline. A typical sampling schedule is after 0, 48, 72, 96, 120, 144, and 168 hours. The concentration of drug in the removed saline solution was determined by liquid scintillation counting or high performance liquid chromatography (HPLC) techniques after each sampling. The flux for each composition was calculated from the terminal linear portions of the curve, plotting cumulative amount penetrated vs time, and is reported in Table II for  
30 each formulation as the average from 4 runs.

Table II also reports the time lag ( $t_0$ ) before reaching steady state delivery of drug to the saline, and the calculated area of skin, that is, the size that a transdermal drug delivery patch would have to be in order to deliver 50 µg of estradiol per day.

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Table I

Test Formulations					
Ingredient*	Concentration (% w/w)				
	I	II	III	IV	V
Estradiol	10.5	5.5	7.0	10.5	5.5
IPA	89.5	23.6	46.5	67.1	—
IBA	—	70.9	46.5	22.4	94.5

40 45 \*IPA = Isopropyl alcohol; IBA = Isobutyl alcohol.

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Table II

Summary of the Results				
Formulation	Flux mcg·cm <sup>-2</sup> hr	t <sub>L</sub> hrs	Avg. Patch size (cm <sup>2</sup> )	
IPA (I)	0.74	46.8	2.8	
75/25 IPA/IBA (IV)	0.82	36.8	2.8	
50/50 IPA/IBA (III)	1.42	36.1	1.5	
25/75 IPA/IBA (II)	0.46	39.0	4.5	
IBA (V)	0.54	40.2	3.9	

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**Claims**

1. A topical composition for the transdermal delivery of a steroid drug which comprises a therapeutically effective amount of a steroid drug in a vehicle comprising a mixture of isopropyl alcohol and isobutyl alcohol, each of these alcohols being present in an amount of from 45% to 55% by weight based on the weight of said mixture.

2. The composition of claim 1 wherein said range is from 47% to 53% by weight.

3. The composition of claim 1 wherein said range is from 49% to 51% by weight.

4. The composition of any one of the preceding claims wherein said steroid drug comprises estradiol.

5. The composition of any one of claims 1 to 4 wherein said steroid drug comprises a progestogen.

6. The composition of claim 5 wherein said progestogen comprises progesterone or medroxy progesterone.

7. The composition of any one of the preceding claims wherein said vehicle further comprises water.

8. The composition of claim 7 wherein said vehicle further comprises methyl cellulose.

9. A transdermal patch for delivering a steroid drug to a patient, wherein the vehicle for said steroid drug comprises a mixture of isopropyl alcohol and isobutyl alcohol, each of these alcohols being present in an amount of from 45% to 55% by weight based on the weight of said mixture.

10. The transdermal patch of claim 9 wherein said vehicle further comprises water.

11. The transdermal patch of claim 10 wherein said vehicle further comprises methyl cellulose.

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DOCUMENTS CONSIDERED TO BE RELEVANT									
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 5)						
Y	US-A-4 775 529 (S.A. SEQUEIRA) * Column 1, lines 20-41; examples; claims * ----	1-11	A 61 K 31/57 A 61 K 47/10 A 61 K 31/565						
Y	S.T.N. FILE SERVER (KARLSRUHE) & CHEMICAL ABSTRACTS, vol. 106, part 10, 9th March 1987, abstract no. 72945s, Columbus, Ohio, US; & JP-A-61 249 934 (NITTO ELECTRIC INDUSTRIAL CO.) 07-11-1986 * Abstract * ----	1-11							
A	EP-A-0 147 146 (AMERICAN HOME PRODUCTS) * Page 9, example 2; claims * -----	1-11							
TECHNICAL FIELDS SEARCHED (Int. Cl. 5)									
A 61 K									
<p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of completion of the search</td> <td style="width: 33%;">Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>29-01-1990</td> <td>BERTE M.J.</td> </tr> </table>				Place of search	Date of completion of the search	Examiner	THE HAGUE	29-01-1990	BERTE M.J.
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<p><b>CATEGORY OF CITED DOCUMENTS</b></p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons &amp; : member of the same patent family, corresponding document</p>									